REMARKS

Claims 4-12 and 14-29 are currently pending. Claims 1 - 3 and 13 have been canceled. Claims 21, 28 and 29 have been amended. Applicants respectfully submit that the amendments to the claims are supported in the specification as originally filed, thus no new matter is presented thereby. Entry of the amendments is respectfully requested.

As a preliminary matter, a number of Information Disclosure Statements have been filed. Specifically, statements were filed on March 5, 2002, May 21, 2002, and June 4, 2002. Another IDS is submitted herewith. Applicants respectfully requests a status update as to the consideration of these disclosure statements. Additionally, the references requested by the Examiner are provided in the enclosed IDS.

Claims 1-2 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite. These claims have been canceled. Applicants respectfully submit that the rejection under 35 U.S.C. 112, second paragraph has been overcome and should be withdrawn.

Claims 28-29 have been rejected under 35 U.S.C. 112, first paragraph as not being commensurate in scope with the specification. In order to expedite prosecution of the instant claims, Applicants have incorporated the Examiner's suggestion by amending claims 28 and 29 to recite that the composition comprises a phospholipid. Applicants respectfully submit that the rejection under 35 U.S.C. 112, first paragraph has been overcome and should be withdrawn.

Claims 1-14 and 16-29 have been rejected under 35 U.S.C. 102 (b) as being anticipated by Edwards et al. This rejection is respectfully traversed for the reasons that follow.

Claim 16 is directed to the inhalation of a dry powder comprising a hydrophobic drug from a passive dry powder inhaler in order to achieve a Tmax within 15 minutes of the inhalation. As such, the present invention is directed to rapid release formulations. The Edwards et al. disclosure is directed to sustained release of an active agent. This is seen in the Edwards et al. disclosure, for example, at p. 8, lines 24-25, p. 15, lines 15-18, and p. 17, lines 16-26. Such disclosure in Edwards et al. is directed to providing prolonged levels of drug for periods of 24 hours or longer. Edwards et al. does not disclose rapid release formulations for inhalation of hydrophobic drugs as claimed. Applicants respectfully submit that this rejection is in error and should be withdrawn.

As amended, claim 21 is directed to an inhalation method for a dry powder composition wherein the emitted dose of said composition exiting from the passive dry powder inhaler after a single inspiratory effort is at least 80% w/w and is substantially independent over an inhalation flow rate of 20-90 l/min and device resistance of 0.04-0.20 $(cmH_2O)^{1/2}$ /L min^{-1}. Edwards et al. discloses that the particulate compositions disclosed therein approach emitted dose efficiencies of almost 80%. Edwards et al. does not disclose compositions exhibiting emitted dose efficiencies of greater than 80% w/w, thus fails to anticipate the invention as currently claimed. Applicant respectfully submits that the rejection is in error and should be withdrawn.

Claim 28 is directed to a method of delivering a therapeutic dose of a bioactive agent to the pulmonary system in a single breath from a passive dry powder inhaler wherein the emitted dose of the particles exiting from the inhaler is at least 80% w/w after a single inspiratory effort. As seen at page 7, lines 17-25, a preferred embodiment of the present invention is directed to the high emitted dose efficiencies achieved by the engineering of the particles according to the present invention. Table 1 of Example 1 demonstrates such high efficiencies wherein the emitted doses reported therein are greater than 80% w/w in all cases. Edwards et al. discloses that the particulate compositions disclosed therein approach emitted dose efficiencies of almost 80%. Edwards et al. does not disclose compositions exhibiting emitted dose efficiencies of greater than 80% w/w, thus fails to anticipate the invention as currently claimed. Applicant respectfully submits that the rejection is in error and should be withdrawn.

Lastly, claim 29 is directed to a method of delivering a therapeutic dose of a bioactive agent to the pulmonary system in a single breath comprising administering particles from a passive dry powder inhaler wherein the fraction of particles having a geometric diameter of less than 3.3 microns is at least 35% w/w after a single inspiratory effort. The respirable fraction data reported in Edwards et al. concerns the fraction of powder collected at stages 2-F of an Anderson Cascade impactor (ACI). As known in the art, this respirable fraction corresponds to that percentage of particles having a size below 5.8 microns. The present invention claims a respirable fraction of greater than 35% w/w as defined by particles having a size less than 3.3 microns. Such a respirable fraction is nowhere disclosed in Edwards et al., thus the rejection is improper and should be withdrawn.

Claims 1-29 have been rejected under 35 U.S.C. 103 as being obvious over Edwards et al. in view of Van Oort et al.

As seen in the specification, a recognized drawback of the prior art is that performance of many dry powder inhalers is dependent upon the patient's inspiratory effort. (See page 2, lines 12-19 of the present specification and Schultz et al.: page 1, lines 21-23). Enclosed herewith are copies of additional publications which further highlight this problem in the art. For example, the article "Lung deposition of budesonide inhaled via Turbuhaler: a comparison with terbutaline sulphate in normal subjects" (1994) concludes that the inspiratory flow has an important effect on lung deposition. Schultz et al. (6,116,237 circa 1996) discloses that in the case of dry powder inhalers, most studies have shown that the major issue surrounding dry powder delivery performance is related to flow rate dependence, at inhalation flow rates ranging from 15 – 120 l/min (col. 1, lines 25-42).

Dunbar et al., "Dispersion and Characterization of Pharmaceutical Dry Powder Aerosols" (1998) further highlights the problem solved by the present invention. Page 18, Section 3. of the Dunbar et al. article discusses mechanisms of dispersion by inhalers. Section 3.1 discusses dispersion in dry powder inhalers and discusses the mechanism of action of several commercial inhalers, including the Spinhaler® device used in Edwards et al. The Dunbar et al. article is later than the Edwards et al. patent filings, and Dunber et al. even refers to the Edwards et al. work in the last paragraph of page 24.

For Dunbar et al. at page 23, first paragraph, it is seen that inhaler performance is a factor of formulation, the inhaler, and the patient. It is stated that emitted dose and fine particle fraction vary depending on patient specific parameters such as inspiratory flow rate. Dunbar et al. go on at page 24, first paragraph, to state the following:

"The air flow generated by the patient' inspiratory effort is, however, the sole source of energy for powder fluidization and dispersion in passive dry powder inhalers. Hence, the accuracy of the dose and the fine particle fraction delivered by these devices depend on the specific resistance of the inhaler and the inspiratory flow rate generated by the patient."

Page 26 of the Dunbar et al. article addresses studies examining emitted dose and fine particle fractions from dry powder inhalers. Dunbar et al. states that the fine particle fraction generally increases with flow rate, the strength of which depends on the formulation and device. Table 4 on page 27 summarizes some of the data.

In contrast to prior efforts to address this problem through device design, the present invention relies upon a particle engineering approach to overcome such issues, as indicated in the specification, for example at page 3, lines 19-26, page 7, lines 5-10, 17-25. For example, Table 1 of Example 1 shows the emitted doses achieved from aerosolization via a number of devices of differing resistances at various inspiratory flow rates. As seen in the table, the emitted doses were in a narrow range. Table 2 of Example 2 shows deposition data where formulations of the present invention resulted in substantially the same deposition whereas prior art formulations varied by almost a factor of two. Tables 4 and 6 also show fine particle fractions achieved via aerosolization via two different devices at various flow rates.

Claim 21 has been amended to recite that the emitted dose of the composition exiting from the passive dry powder inhaler after a single inspiratory effort is at least 80% w/w and is substantially independent over an inhalation flow rate of 20-90 l/min and device resistance of 0.04-0.20$(cmH_2O)^{1/2}$ /L min^{-1}. As discussed above, Edwards et al. discloses that the compositions disclosed therein provide for emitted doses approaching 80%. Van Oort discloses hollow particulates as noted by the Examiner. However, van Oort is silent as to the aerosol performance of the compositions disclosed therein. Similarly, claims 28 and 29 recite methods for administering aerosols with specific performance characteristics.

As discussed above, there is a recognized problem in the field of the present invention with respect to aerosol performance in passive dry powder inhalers. The present invention has overcome these limitations of the prior art and represents a significant advance in the field. The Examiner has not cited any teachings, above or in combination, which disclose or suggest the superior aerosol performance as recited in claims 21, 28, and 29. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness and the rejection should be withdrawn.

Claim 16 recites inhaling the drug composition from the inhaler in order to achieve a Tmax within 15 minutes of the inhalation. As discussed above, Edwards et al. is directed to sustained release. Van Oort is silent as to administration profiles of the compositions to be administered according to the teachings therein. Thus, the Examiner has failed to set forth a *prima facie* case of obviousness with respect to claim 16, particularly in view of the fact that Edwards et al. teaches away from the present invention. Accordingly, the Examiner has failed to

present a *prima facie* case of obviousness with respect to claim 16 and the rejection should be withdrawn.

CONCLUSION

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Applicants believe that all the pending claims are presently in condition for allowance. However, the Examiner is invited to telephone the undersigned attorney at the number below if it is believed that this will expedite prosecution of the present application.

Respectfully submitted,

Dated: 9/23/02

By: _____

Michael J. Rafa.
Registration No. 38,740
Attorney of Record
(650) 631-5053

Version with markings to show changes made

Claims 1- 3 and 13 have been canceled.

21. A method for inhalation of a dry powder drug comprising:

administering a dry powder drug composition comprising particles comprising a phospholipid matrix and a particle size of 1-30 microns, mass median aerodynamic diameter of less than 5 microns, and bulk density of less than 0.5 g/cm^3 from a passive dry powder inhaler wherein the emitted dose of said composition exiting from said passive dry powder inhaler after a single inspiratory effort is at least [6]80% w/w and is substantially independent over an inhalation flow rate of 20-90 l/min and device resistance of 0.04-0.20$(cmH_2O)^{1/2}$ /L min^{-1}.

28. A method of delivering a therapeutic dose of a bioactive agent to the pulmonary system in a single breath, comprising:

administering particles comprising a phospholipid and a bioactive agent from a passive dry powder inhaler wherein the emitted dose of said particles exiting from said inhaler is at least 80% w/w after a single inspiratory effort.

29. A method of delivering a therapeutic dose of a bioactive agent to the pulmonary system in a single breath, comprising:

administering particles comprising a phospholipid and a bioactive agent from a passive dry powder inhaler wherein the fraction of particles having a geometric diameter of less than 3.3 microns administered from said inhaler is at least 35% w/w after a single inspiratory effort.